Dear Colleagues

**Codeine use in children, particularly following tonsillectomy and/or adenoidectomy**

**Publications from regulatory bodies**

Recent publications from regulatory bodies in the U.S., Europe and the UK have necessitated a review of codeine prescribing practice. In February 2013 the U.S. Food and Drug Administration (FDA) released a Safety review update of codeine use in children. It implicated codeine in 3 deaths and one life threatening event in children following tonsillectomy and/or adenoidectomy for obstructive sleep apnoea (OSA) despite having been given within prescribed limits. The FDA has warned healthcare professionals not to use codeine for these procedures. The full report may be read at [www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf).

The European Medicine Agency (EMA) undertook a further review and published “Restrictions on the use of codeine for pain relief in children” on 28 June 2013. The EMA’s report stated that codeine is contraindicated in all persons below 18 years for pain relief following surgery to remove the tonsils or adenoids for OSA. It went further on to stipulate that codeine should only be given to children greater than 12 years old if pain cannot be relieved by other analgesics such as paracetamol and ibuprofen and then only at the lowest effective dose for the shortest period of time. The full report may be found here: [www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144851.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144851.pdf).

Following this the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK produced drug safety advice entitled “Codeine for analgesia: restricted use in children because of reports of morphine toxicity” in their July 2013 Drug Safety Update, which may be read at the following link: [www.mhra.gov.uk/home/groups/dsu/documents/publication/con296410.pdf](http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con296410.pdf). This upheld the EMA’s stance on the use of codeine.

These publications have led to a substantial amount of debate among professional bodies including the Association of Paediatric Anaesthetists (APA) and the Neonatal and Paediatric Pharmacists Group (NPPG). Locally and nationally there has been some confusion about analgesia following these ENT procedures and also about the use of codeine in children in general. The regulatory bodies, although producing directives about withholding codeine use they unfortunately did not suggest suitable safe and practical alternatives, leading to Trust’s making local arrangements rather than following a national consensus.

**Pharmacology of codeine**

Codeine is a prodrug and its analgesic properties are based on its metabolism to morphine. This is dependent on CYP2D6 (a member of the cytochrome P450 system) enzymatic conversion. This is subject to significant genetic variation and therefore enzyme activity. The concern is that certain individuals carry forms of the gene for CYP2D6 that make them fast metabolisers (ultra-rapid metabolisers), leading to accelerated production of morphine and accumulation. Patients with OSA have altered respiratory drive and therefore maybe particularly susceptible.
There is significant variation in the prevalence of ultra-rapid metabolisers among ethnic groups. Patients with an African or Ethiopian background are at particular risk. The incidence among Caucasians maybe up to 6.5%. The following table is taken from the MHRA publication.

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence of ultra-rapid metabolisers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African or Ethiopian</td>
<td>29.0%</td>
</tr>
<tr>
<td>African American</td>
<td>3.4–6.5%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2–2.0%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.6–6.5%</td>
</tr>
<tr>
<td>Greek</td>
<td>6.0%</td>
</tr>
<tr>
<td>Hungarian</td>
<td>1.9%</td>
</tr>
<tr>
<td>Northern European</td>
<td>1.0–2.0%</td>
</tr>
</tbody>
</table>

**Local consensus to Codeine Prescribing**

Following consultation by the paediatric pain service with representatives from pharmacy, ENT and paediatric surgeons, paediatric anaesthetists, paediatricians and the emergency department, a pragmatic consensus has been reached. This reflects national guidance and practice at children’s hospitals nationally. It falls into two parts; 1) analgesia for tonsillectomy and/or adenoidectomy and 2) Codeine use in other children.

**Analgesia following Tonsillectomy and/or Adenoidectomy**

- Codeine should no longer be prescribed for any child less than 18 years having surgery for removal of their tonsils or adenoids for all indications.
- Regular paracetamol and a suitable NSAID drug if not contraindicated remain the mainstay of treatment for pain.
- Suitable alternatives for breakthrough pain relief have been evaluated in terms of formulation and suitability for take home analgesia. It should be stressed that the improved safety of other alternatives such as oral morphine, tramadol and oxycodone has not been established. Experience is limited. All opioids should be given on an 'as required' basis at the lowest effective dose for the shortest duration.
- Dihydrocodeine is suggested as a suitable alternative to codeine. It is significantly less reliant on metabolism to produce its analgesic effects and is available as an oral solution 10mg/5ml. However this should not be given to children less than one year of age due to the alcohol content. The dose is comparable to codeine, being given at a dose of 0.5mg/kg (maximum 30mg) as required every 4-6 hours, with a maximum of 4 doses in a 24 hour period. This may be increased to 1mg/kg (maximum 30mg) if the lower dose is insufficient in children older than 4 years old. Dihydrocodeine is also available as 30mg tablets. The MHRA specifically state that dihydrocodeine is excluded from its directive on codeine.
- Pharmacy has arranged an appropriate stock of dihydrocodeine on the wards and recovery areas. Small bottles of dihydrocodeine will be available for breakthrough pain for children to take home.
- Other analgesics may be suitable, particularly for children who can swallow tablets e.g. tramadol. Clinicians should exercise their judgment about appropriate opioids to take home given individual circumstances. All opioids have potential risk and should be given at the lowest effective dose for the shortest duration.
Codeine use in other children

- Despite the EMA and MHRA’s publications stating that codeine should not be used in children under 12 years old, codeine continues to be widely used by some children’s hospitals in the UK.
- Codeine is commonly used in paediatric practice. However prescribers should be aware that its continued use will be outside of the recommendations of the MHRA and will be prescribing it beyond its licence. The potential benefits and risks should be carefully considered for each child.
- Professional bodies, including the APA have responded. The full response may be read at www.apagbi.org.uk/sites/default/files/images/Codeine%20and%20Paracetamol%20final%20V2.pdf. This statement reiterates the APA guidelines on the use of codeine within the “Good Practice in Postoperative and Procedural Pain” 2nd edition 2012 guidelines.
- Codeine should not be prescribed to a person of any age known to be a CYP2D6 ultra-rapid metaboliser.
- Codeine should be used at the lowest effective dose for the shortest possible period.
- A history of a child’s previous experience with codeine should be sought. However there is no guarantee that a child has had codeine uneventfully will continue to do so.
- The initial dose should be 0.5mg/kg (maximum 30mg), at 6 hour intervals as required, with a maximum of 4 doses in a 24 hour period. The dose should only be increased to 1mg/kg (maximum dose 60mg) if the lower dose is proven not to be effective.
- Most children should only require a dose of 0.5mg/kg for take home analgesia and this should be used with caution. Information should be given to parents and carers on how to recognise the symptoms and signs of morphine toxicity and the appropriate action they should take.
- Codeine is not recommended for children whose breathing may be compromised, including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections and multiple trauma. The symptoms of morphine toxicity may be increased in these settings.

It is likely that new national guidance will be presented in the coming months and this local guidance may then be reviewed.

Yours sincerely

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